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09/647,004	11/29/2000	Steen Oestergaard	OSTERGAARD1	3933

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EXAMINER	
BARTON, JEFFREY THOMAS	

ART UNIT	PAPER NUMBER
1753	

DATE MAILED: 10/19/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

AC

Office Action Summary	Application No.	Applicant(s)	
	09/647,004	OESTERGAARD ET AL.	
	Examiner	Art Unit	
	Jeffrey T. Barton	1753	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 December 2000*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-80* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-80* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *20001218*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Specification

1. The disclosure is objected to because of the following informalities:

a. On page 13 at lines 26-31, it appears that some unit prefixes were omitted, since some listed speeds seem unlikely. (e.g. 100 m/s)

Appropriate correction is required.

Claim Objections

2. Claim 61 is objected to because it is a method claim amended to be dependent on the device claim 1. Claim 61 is treated herein as being dependent on claim 25, as fits the pattern of the preliminary amendment. Appropriate correction is required.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 12 and 50 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the

invention. No description of an embodiment using centrifugation was described, and it is not clear how such a device would function.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 1-8, 14-40, 42-46, and 52-80 are rejected under 35 U.S.C. 103(a) as being unpatentable over Southgate et al. (U.S. 5,863,801)

Addressing claims 1 and 24:

Southgate et al disclose a microsystem (Column 13, lines 8-12) comprising linked compartments (Figure 9) wherein a reagent immobilized on a particle can contact an analyte in a liquid carrier (Column 18, lines 43-56; Column 21, line 59 - Column 22, line 37), the system comprising: compartments defined by walls and openings for liquid passage (Figure 9); means for subjecting at least part of the system to a field to move particles between first and second compartments (Column 16, lines 25-60); a passage defined between the first and second compartments (e.g. passage between 1113 and 1112 in Figure 9) so as to allow at least one particle to be moved through the passage between the compartments, which contain different fluids (e.g. wash buffers, lysis solutions; Figure 9; Column 16, lines 25-60).

Additionally relevant to claim 24, Southgate et al disclose a method of moving a particle between compartments of a microsystem (Column 21, line 59 - Column 22, line 37), the method comprising the steps of: introducing the particle and a liquid carrier into the first compartment (Column 22, lines 15-31), introducing a second liquid carrier into a second compartment (Column 22, lines 32-34), subjecting the microsystem to a field

exerting a force on the particles susceptible to the field (Column 22, lines 15-18; Column 16, lines 25-60), and moving the particles between chambers by means of the force. (Column 16, lines 25-60)

Southgate et al do not explicitly disclose moving the particles between compartments with substantially no transfer of the respective liquids between compartments.

However, Southgate et al disclose using an external permanent magnet to secure or move particles within the chambers and channels of their device, without requiring simultaneous fluid flow. (Column 16, lines 25-60)

It would have been obvious to one having ordinary skill in the art at the time the invention was made to use this permanent magnet to move the magnetic particles between chambers of the device for reaction (e.g. lysis), because Southgate et al disclose this as an alternative means of transporting the particles. Given the disclosed size of the particles (Column 16, lines 18-24) and channels (Column 13, lines 8-12), the fluid flow caused by particle motion (i.e. friction, turbulence) would be similar to that of the claimed system.

The crux of the invention as disclosed appears to be the ability to transfer particles within the device without simultaneous fluid transfer. The specification describes this in terms of minimization of Rayleigh number by providing channels with narrow cross-section in order to suppress convection. It appears that any previously known microfluidic system with comparable channel dimensions would similarly inhibit convection. The specification also describes the production of particle motion by

application of a field that causes their motion without causing general fluid motion. Such motion is generally seen in electrophoresis (though not typically with beads), particularly in devices constructed specifically for reduction or elimination of electroosmotic flow. (e.g. Soane et al) It appears that no significant fluid flow will be caused by particle motion if there is a large enough difference between the particle size and the channel/compartment cross-section. Examples involving motion of beads caused by an applied field can be found in Southgate et al as discussed above, Parton et al (dielectrophoresis), and Wickramasinghe et al. (electric/magnetic fields)

Addressing the dependent claims:

Relevant to claims 2, 3, and 5, Southgate et al disclose particles with surfaces suitable for immobilizing reagents, reagents suitable for such immobilization, and analytes capable of reaction with this immobilized reagent. (Column 18, lines 43-56)

Relevant to claim 4, Southgate et al disclose a bead storage compartment. (Figure 9, 1113)

Relevant to claim 6, Southgate et al disclose a second compartment with an opening for passing fluids to/from the device exterior. (Figure 9, 1104)

Relevant to claims 7, 8, 45, and 46, Southgate et al disclose positioning a permanent magnet for applying a magnetic field to a part of the system. (Column 16, lines 25-60)

Claims 14, 15, 18, 19, 23, 30, 52, 53, 58, and 78-80 are directed to means and methods of detection (specifically optical detection) within the device that are conventional, and obvious to include in such an analytical device.

Relevant to claims 16 and 54, Southgate et al disclose an auxiliary compartment with an opening to the exterior and a passage to the other compartments (Figure 9, 1104)

Relevant to claim 17, the permanent magnet of Southgate et al can be moved back and forth. (Column 16, lines 25-60)

Relevant to claims 20, 21, 59, and 60, Southgate et al disclose particles of 25 micron diameter (Column 16, lines 18-24), and use of different diameter particles would be an obvious modification.

Relevant to claim 22, Southgate et al disclose a device made from non-magnetic materials. (Column 12, lines 40-52)

Relevant to claims 25-27, 32, and 33, Southgate et al disclose the first or second liquid carrier comprising analyte, contacting the analyte with a reagent immobilized on a particle, and moving a particle between compartments with different fluid carriers. (Column 18, lines 43-56; Example 4)

Relevant to claims 28 and 29, Southgate et al disclose wash buffer in device compartments (Figure 9), which would be obvious to use.

Relevant to claim 31, the methods of Southgate et al use aqueous fluids throughout, and thus the wash buffer will effectively remove any liquid of the system, despite possible contamination.

Relevant to claim 34, Southgate et al disclose most liquid carriers being prepackaged on the device (Column 23, lines 3-7), which would be prior to a later-injected reagent contacting the beads.

Relevant to claim 35, Southgate et al disclose simultaneous carrier and particle introduction to the first compartment. (Column 22, lines 15-31)

Relevant to claim 36, Southgate et al disclose sequential fluid and bead introduction. (Example 5)

Relevant to claim 37, any particle is disposable, broadly defined.

Relevant to claims 38-40, Southgate et al disclose reconstitution of freeze-dried samples. (Column 11, lines 11-24)

Relevant to claims 42 and 43, Southgate et al disclose aqueous liquid carriers. (Example 4)

Relevant to claim 44, Southgate et al disclose analysis of DNA. (Column 18, lines 43-56)

Relevant to claims 54-56, Southgate et al disclose a several interconnected chambers (Figure 9), magnetic means of causing particle motion (Column 16, lines 25-60), and secondary interactions (e.g. staining in Example 5) that would be obvious to perform in a secondary compartment of Figure 9.

Relevant to claim 57, Southgate et al disclose compartments containing wash buffer, and the means of moving particles to these chambers. (Figure 9; Column 18, lines 25-60)

Claims 61-74 are directed to specific analytes that are typical objects of analysis, and it would be obvious to use the claimed device and method in analyzing them. See Southgate et al, Column 10, lines 17-55)

Relevant to claims 75 and 76, Southgate et al disclose thermal cycling with amplification and denaturation. (Example 5)

Relevant to claim 77, Southgate et al disclose performing their methods using a device that is obvious to modify to correspond to claim 1, as discussed above.

9. Claims 9 and 47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Southgate et al (U.S. 5863,801) in view of Allen et al.

Southgate et al disclose a device and method corresponding to claims 7 and 45, as described above.

Southgate et al do not explicitly disclose using an electromagnet.

Allen et al disclose a microfluidic device that uses integrated electromagnets to manipulate magnetic particles. (Abstract)

It would have been obvious to one having ordinary skill in the art at the time the invention was made to further modify the device and method of Southgate et al by replacing the movable permanent magnet with integrated plural electromagnetic elements, as taught by Allen et al, because it would provide a self-contained system.

10. Claims 10 and 48 rejected under 35 U.S.C. 103(a) as being unpatentable over Southgate et al (U.S. 5863,801) in view of Wickramasinghe et al.

Southgate et al disclose a device and method corresponding to claims 7 and 45, as described above.

Southgate et al do not explicitly disclose using electrodes in contact with the fluids to generate an electric field to cause particle motion by electrophoresis.

Wickramasinghe et al disclose a microfluidic device that uses electrodes to cause electrophoretic motion of magnetic particles. (Column 17, line 65 - Column 18, line 18)

It would have been obvious to one having ordinary skill in the art at the time the invention was made to further modify the device and method of Southgate et al by replacing the movable permanent magnet with electrodes that generate an electric field to cause electrophoretic movement of the magnetic particles, as taught by Wickramasinghe et al, because it would provide a self-contained system.

11. Claims 11 and 49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Southgate et al in view of Parton et al.

Southgate et al disclose a device and method corresponding to claims 7 and 45, as described above.

Southgate et al do not explicitly disclose using electrodes near the fluids to generate an electric field to cause particle motion by dielectrophoresis.

Parton et al disclose a method of causing particle motion using a plurality of electrodes close to a channel to generate electric fields that cause movement of dielectric particles in the fluid within the channel. (Abstract)

It would have been obvious to one having ordinary skill in the art at the time the invention was made to further modify the device and method of Southgate et al by replacing the magnetic particles with dielectric particles and replacing the movable permanent magnet with a plurality of electrodes that generate an electric field to cause dielectrophoretic movement of the particles, as taught by Parton et al, because it would provide a more controllable, self-contained system.

12. Claims 13 and 51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Southgate et al (U.S. 5863,801) in view of Blankenstein. (Citation AG on 1449)

Southgate et al disclose a device and method corresponding to claims 7 and 45, as described above.

Southgate et al do not explicitly disclose using a gravitational field to cause particle motion.

Blankenstein discloses a microfluidic system that uses gravitational force to cause movement of particles. (Page 1, lines 5-10; Summary section)

It would have been obvious to one having ordinary skill in the art at the time the invention was made to further modify the device and method of Southgate et al by removing the movable permanent magnet and using device orientation and gravity to provide particle movement, as taught by Blankenstein, because it would eliminate the need for a dedicated field generator.

13. Claim 41 is rejected under 35 U.S.C. 103(a) as being unpatentable over Southgate et al in view of Ross.

Southgate et al disclose a method corresponding to claim 38, as described above.

Southgate et al do not explicitly disclose analyzing a cryoprotected sample.

Ross discloses an assay method that analyzed samples that had previously been cryoprotected. (Column 5, lines 19-21)

It would have been obvious to one having ordinary skill in the art at the time the invention was made to further modify the method of Southgate et al by using previously-cryoprotected samples, as taught by Ross, because it would allow analysis of living samples at the investigator's convenience.

14. Claims 1-9, 13-40, 42-47, and 51-80 are rejected under 35 U.S.C. 103(a) as being unpatentable over Blankenstein (Citation AG on 1449) in view of Southgate et al. (U.S. 5,863,801)

Addressing claims 1 and 24:

Blankenstein discloses a microsystem (Figure 11) wherein a reagent immobilized on a particle can contact an analyte in a liquid carrier (Page 10, lines 11-17) the system comprising: compartments defined by walls and openings for liquid passage (Figure 11); means for subjecting at least part of the system to a field to move particles between first and second compartments (magnet 8); so as to allow at least one particle to be

moved through the passage, with substantially no fluid flow. (Page 10, lines 11-17; Page 25, line 36 - Page 26, line 5) The system is also disclosed as optionally comprising compartments. (Figures 5, 7, 10, for example)

Additionally relevant to claim 24, Blankenstein discloses a method of moving a particle within a microsystem (Page 10, lines 11-17; Page 25, line 36 - Page 26, line 5), the method comprising the steps of: introducing the particle and a liquid carrier into the compartment, subjecting the microsystem to a field exerting a force on the particles susceptible to the field, and moving the particles within the channel by means of the force. (Page 10, lines 11-17; Page 25, line 36 - Page 26, line 5)

Blankenstein does not explicitly disclose moving the particles by means of a field between compartments with different liquid carriers.

Southgate et al disclose a micro system comprising several interconnected compartments, and the use of an external permanent magnet to secure or move particles within the compartments and channels of their device, without requiring simultaneous fluid flow. (Figure 9; Column 16, lines 25-60)

It would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the device and method of Blankenstein by providing the device with several chambers containing different reagents (as taught by Southgate et al) and using the magnetic field to cause migration of the particles between these chambers, because it would allow accumulation of more information about the analytes. Given the disclosed size of the particles (Table 2) and channels (Page 6, lines 8-12),

the fluid flow caused by particle motion (i.e. friction, turbulence) would be similar to that of the claimed system.

The crux of the invention as disclosed appears to be the ability to transfer particles within the device without simultaneous fluid transfer. The specification describes this in terms of minimization of Rayleigh number by providing channels with narrow cross-section in order to suppress convection. It appears that any previously known microfluidic system with comparable channel dimensions would similarly inhibit convection. The specification also describes the production of particle motion by application of a field that causes their motion without causing general fluid motion. Such motion is generally seen in electrophoresis (though not typically with beads), particularly in devices constructed specifically for reduction or elimination of electroosmotic flow. (e.g. Soane et al) It appears that no significant fluid flow will be caused by particle motion if there is a large enough difference between the particle size and the channel/compartment cross-section. Examples involving motion of beads caused by an applied field can be found in Southgate et al as discussed above, Parton et al (dielectrophoresis), and Wickramasinghe et al. (electric/magnetic fields)

Addressing the dependent claims:

Relevant to claims 2, 3, and 5, Blankenstein discloses particles with surfaces suitable for immobilizing reagents, reagents suitable for such immobilization, and analytes capable of reaction with this immobilized reagent. (Magnetic beads)

Relevant to claims 7-9 and 45-47 Blankenstein discloses positioning a permanent magnet or electromagnet for applying a magnetic field to a part of the system. (Figure 11; magnet 8; Page 10, lines 31-38)

Relevant to claims 13 and 51, Blankenstein discloses using a gravitational field to cause particle movement. (Page 1, lines 5-10)

Claims 14, 15, 18, 19, 23, 30, 52, 53, 58, and 78-80 are directed to means and methods of detection (specifically optical detection) within the device that are conventional, and obvious to include in such an analytical device. For example, see Figures 2, 7, 16 of Blankenstein and the respective descriptions in the specification, also page 9, lines 4-13.

Claims 61-74 are directed to specific analytes that are typical objects of analysis, and it would be obvious to use the claimed device and method in analyzing them. See Southgate et al, Column 10, lines 17-55)

Regarding other dependent claims listed at the head of this paragraph, all appear to be conventional features of microfluidic devices and methods, disclosed by or obvious in view of Southgate et al as described above in paragraph 8.

15. Claims 10, 11, 41, 48 and 49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Blankenstein and Southgate et al as applied to claims 7, 38, and 45 above, and further in view of either Wickramasinghe et al (10 and 48), Parton et al (11 and 49), or Ross (41).

The material disclosed by the respective references and motivations for their combination are as given above in paragraphs 10, 11, and 13.

Conclusion

16. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Wilding et al (U.S. 5,637,469 - Related to reference AE on 1449) disclose a similar device and method that uses an external magnetic field to cause bead movement, without specific motion of surrounding fluids.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Jeffrey Barton, whose telephone number is (571) 272-1307. The examiner can normally be reached Monday-Friday from 8:30 am – 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Nam Nguyen, can be reached at (571) 272-1342. The fax number for the organization where this application or proceeding is assigned is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should

you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at (866) 217-9197 (toll-free).

JTB
October 13, 2004

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